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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/604,325	06/26/2000	Kriszina M. Zsebo	01017/32953A	6723

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/10/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/604,325	ZSEBO ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments 26 June 2000 (Paper No. 1), 09 January 2002 (Paper No. 6), 30 January 2002 (Paper No. 7), and 17 June 2002 (Paper No. 10) have been entered in full. Claims 1-70 are cancelled and claims 71-96 are added.

Please note that there are no claims 71-78 in the originally filed application and 37 CFR § 1.126 has been applied to renumber the claims in consecutive order. Claims 79-104 (filed 09 January 2002, Paper No. 6) have been renumbered as claims 71-96.

Applicant's election without traverse of new Group IX, claims 71-96, in Paper No. 6 (09 January 2002) is acknowledged.

Claims 71-96 are under consideration in the instant application.

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. *Specifically, the claims recite figure numbers rather than sequence identifiers.* Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Specification

2. The disclosure is objected to because of the following informalities:

(2a.) An updated status of the parent nonprovisional applications should be included in the first sentence of the specification.

(2b.) The specification is replete with references to U.S. patent Application Nos. The specification should include an updated status of these applications. For example, see pg 24 and 182.

(2c.) The Brief Description of the Drawings fails to refer to Figures 24A-24B; Figures 29A-29B; Figures 30A-30B; Figures 42A, 42B, 42C, 42D; Figures 44A, 44B, 44C; Figures 56A, 56B.

(2d.) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF STIMULATING GROWTH OF MELANOCYTE PRECURSOR CELLS AND TREATMENT OF A PIGMENTATION DISORDER BY ADMINISTERING STEM CELL FACTOR".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 71-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 71-96 are directed to a method of stimulating growth of melanocyte precursor cells in a human and a method of treating a pigmentation disorder in a human comprising administering to the human a therapeutically effective amount of a human stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier. The claims recite that the SCF polypeptide is selected from the group consisting of amino acids 1-162, 1-164, and 1-165 as set out in Figure 15C. The claims recite that the SCF polypeptide consists of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164, 2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 as set out in Figure 42A-C. The claims recite that the SCF polypeptide consists of amino acids 1-152, 1-157, 1-160, 1-161, and 1-220 as set ou in Figure 44A-C. Additionally, the claims recite that the stem cell factor is co-administered with at least one or more cytokines selected from a group consisting of IL-1, IL-2, Il-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF. The claims recite that the pharmaceutically acceptable carrier is suitable for topical delivery, oral delivery, parenteral delivery, pulmonary delivery, and nasal delivery.

The specification teaches several experiments in which mice, rats, baboons, and dogs are intravenously or subcutaneously administered SCF alone or SCF in combination with other cytokines (pg 105-110, 151-168). The peripheral blood and bone marrow removed from the subjects is monitored for such cells as red blood cells, platelets, and white blood cells. The specification also teaches that the effect of SCF on survival of mice after lethal irradiation is measured. However, the specification also does not teach any methods or working examples that stimulate the growth of melanocyte precursor cells in any subject, particularly a human, by

administration of SCF alone or in combination with a cytokine. Although the experiments in the specification monitor the numbers of numerous cell types, melanocyte precursor cells are not one of the cell types examined. Furthermore, the skilled artisan would not be able to predict the effects of administration of a SCF polypeptide or SCF-cytokine composition since it cannot be determined from the specification of the instant application or the claims which specific melanocyte precursor cells in the body are being targeted for the stimulation of growth. Longley et al. (J Invest Dermatol 113(1): 1390-140, 1999; see pg 139, bottom of col 1) state that the epidermal membrane-bound form of SCF is sufficient and necessary for normal melanocyte function in the epidermis. However, soluble SCF is associated with hyperfunction of melanocytes (Longley; pg 139, bottom of col 1). Therefore, one skilled in the art would not be able to predict the effect of the soluble SCF of the instant application if administered to patients. Undue experimentation would also be required of one skilled in the art to determine the efficacy of growth of melanocyte precursor cells in a subject by administration of a SCF or a SCF-cytokine composition. Furthermore, the specification does not teach any methods or working examples that treat a pigmentation disorder, particularly melanocytopenia (i.e., vitilago or piebaldism), by administration of SCF alone or in combination with a cytokine to a human. Undue experimentation would also be required of the skilled artisan to determine efficacy of therapy for pigmentation disorders because the specification of the instant application and the claims do not recite how SCF is supposed to treat the disorder. For example, will SCF increase skin pigmentation? Will SCF increase hair pigmentation? Will SCF increase the number of melanocytes or alter the development of melanocytes? Additionally, a large quantity of

experimentation would be necessary to determine the optimal administration route, dosage, frequency, and duration of the treatment of SCF in a human subject.

Relevant literature also reports that the goal of delivering proteins and peptides noninvasively has only achieved modest success, with poor applicability to proteins and peptides (pg 343, col 1-2; Pettit et al. Trends Biotechnol 16: 343-349, 1998). The problems posed by proteins and peptides is their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, limited success has been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical instability (pg 344-345). Much effort has been given to the transdermal delivery of pharmaceutical products, but clinical applications have been limited to non-protein drugs because of the skin's poor permeability to proteins and peptides (pg 343, col 2). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Although the pulmonary delivery route has generated the most encouraging data, the bioavailability of proteins (i.e. the amount of protein that crosses from the alveoli in to the pulmonary circulation) is dependent on the physical characteristics of the delivered protein and is not the same for proteins and peptides in general (pg 343-344). Therefore, the state of the prior art establishes the unpredictability of delivering proteins to a subject.

Furthermore, undue experimentation would be required of the skilled artisan to administer all the SCF polypeptide fragments recited in the claims to a subject and determine the growth of melanocyte precursor cells and efficacy of therapy of treating a pigmentation disorder. Undue experimentation would also be required of the skilled artisan to administer all possible combinations of SCF polypeptide fragments with one or more cytokines to a human and determine the growth of melanocyte precursor cells and efficacy of therapy of treating a pigmentation disorder. Regarding the numerous SCF polypeptide fragments, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized

procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate SCF polypeptides that stimulate growth of melanocyte precursor cells and treat a pigmentation disorder as well as to determine the efficacy of treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of protein administration to a subject, and the breadth of the claims which fail to recite any specific type or region of melanocyte precursor cells targeted for growth stimulation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 77 and 83-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 78 and 83-84, the acronyms "IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Grichnik et al. J Invest Dermatol 111 : 233-238, 1998.

Sieberblum M. Biochemistry and Cell Biology-Biochimie et biologie cellulaire 76(6): 1039-1050, 1998.

Vancoillie et al. Eur J Dermatol.;9(3):241-251, 1999.

Nishikawa et al. EMBO J 10(8) : 2111-2118, 1991.

Spritz RA. Semin Cutan Med Surg. 16(1):15-23, 1997.

Morrison-Graham K. Dev Biol. 159(1):346-352, 1993.

Murphy et al. Dev Biol. 153(2):396-401, 1992.

MacKenzi et al. Dev Biol 192 : 99-107, 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
September 3, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER